Bariatric Arterial Embolization: Effect of Microsphere Size on the Suppression of Fundal Ghrelin Expression and Weight Change in a Swine Model

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Conflicts of interest are listed at the end of this article.

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Purpose: To determine whether microsphere size effects ghrelin expression and weight gain after selective bariatric arterial embolization (BAE) in swine.

Materials and Methods: BAE was performed in 10 swine by using smaller (100–300 μm; $n = 5$) or larger (300–500 μm; $n = 5$) calibrated microspheres into gastric arteries. Nine control pigs underwent a sham procedure. Weight and fasting plasma ghrelin levels were measured at baseline and weekly for 16 weeks. Ghrelin-expressing cells (GECs) in the stomach were assessed by using immunohistochemical staining and analyzed by using the Wilcoxon rank-sum test.

Results: In pigs treated with smaller microspheres, mean weight gain at 16 weeks (106.9% ± 15.0) was less than in control pigs (131.9% ± 11.6) ($P < .001$). Mean GEC density was lower in the gastric fundus (14.8 ± 6.3 vs 25.0 ± 6.9, $P < .001$) and body (27.5 ± 12.3 vs 37.9 ± 11.8, $P = .004$) but was not significantly different in the gastric antrum (28.2 ± 16.3 vs 24.3 ± 11.6, $P = .84$) and duodenum (9.2 ± 3.8 vs 8.7 ± 2.9, $P = .66$) versus in control pigs. BAE with larger microspheres failed to suppress weight gain or GECs in any stomach part compared with results in control swine. Plasma ghrelin levels were similar between BAE pigs and control pigs, regardless of microsphere size. Week 1 endoscopic evaluation for gastric ulcers revealed none in control pigs, five ulcers in five pigs embolized by using smaller microspheres, and three ulcers in five pigs embolized by using larger microspheres.

Conclusion: In bariatric arterial embolization, smaller microspheres rather than larger microspheres showed greater weight gain suppression and fundal ghrelin expression with more gastric ulceration in a swine model.

Obesity (body mass index [BMI] ≥ 30) has become a global health epidemic affecting more than 600 million people (1). Obesity is a leading contributor to mortality, morbidity, disability, and health care utilization and costs in the United States (2). Nonsurgical treatments, including lifestyle changes and pharmacologic interventions, have been ineffective in curbing the increase in the number of overweight and obese individuals. Currently, only bariatric surgery, including Roux-en-Y gastric bypass, adjustable gastric banding, and sleeve gastrectomy, has produced substantial benefit for people with severe obesity (BMI ≥ 40). However, only 1% of eligible patients elect to undergo bariatric surgery, presumably because of the high cost, inadequate insurance coverage, and concerns regarding complications (3,4). Thus, a less invasive intervention is desirable.

Obesity is a complex, multifactorial disease, and it is closely related to appetite regulation (5). Among the gastrointestinal metabolic hormones that maintain energy expenditure and homeostasis (4,6), ghrelin is the only hormone known to potently stimulate appetite (7). Ghrelin is a 28–amino acid peptide hormone produced by cells predominately distributed in the fundal region of the stomach in humans and other monogastric animals (8–10). Multiple pharmacologic approaches to modulate ghrelin production have been attempted, such as the delivery of ghrelin antagonists or ghrelin vaccines. However, none has been clinically effective for weight management, to our knowledge (11–13). Results of previous studies (14–16) suggest that weight loss in patients who undergo the most effective bariatric surgery does not depend solely on stomach volume restriction but can also be attributed to exclusion of the ghrelin-producing fundus. Given the unique distribution and function of ghrelin, selective embolization of the gastric fundus may suppress ghrelin production and, thus, lead to weight loss.

Since the initial introduction of bariatric arterial embolization (BAE) (17), several preclinical studies have shown that BAE performed by using a liquid sclerosing agent (17,18), microspheres (19,20), or a combination of microspheres with coils (21), can result in weight loss or reduced weight gain and decreased systemic ghrelin production for up to 8 weeks in large animals. Recently, BAE has entered clinical trials for severely obese humans with promising early results (11,22–24). However, to our knowledge, no study has assessed the effect of microsphere

Abbreviations

BAE = bariatric arterial embolization, BMI = body mass index, GEC = ghrelin-expressing cell

Summary

Smaller embolic microspheres were more effective than larger microspheres at reducing weight gain and suppressing gastric fundal and body ghrelin expression without inducing upregulation of ghrelin-expressing cells elsewhere in the swine stomach for 16 weeks.

Implications for Patient Care

- Image-guided bariatric arterial embolization could provide a nonsurgical means to achieving weight loss.
- Although the "ideal" size of embolic microspheres still needs to be determined, to our knowledge, it appeared that smaller (100- to 300-μm) microspheres produced greater weight loss than did larger (300- to 500-μm) microspheres in a swine model.

size on the suppression of ghrelin production and weight loss beyond 8 weeks.

The purpose of this study was therefore to determine whether different sizes of commercially calibrated microspheres used for selective BAE cause substantially different gastric ghrelin expression, weight gain, and mucosal injury during a 16-week period in swine.

Materials and Methods

Embolic microspheres (Embospheres) were provided by Merit Medical Systems (South Jordan, Utah). The authors had complete control of the data and information submitted for publication. The study was approved by our institution's animal care and use committee.

Selective BAE

Nineteen healthy, growing female Yorkshire swine (mean weight, 24.1 kg ± 2.9 [standard deviation]) were recruited during two phases separated by more than 4 months. To minimize confounding factors, such as genetic differences, seasonal changes, and differences in shipping and handling, each phase of the study had its own controls. Phase I included 10 pigs, which were randomized to undergo embolization with larger microspheres (300–500 μm) (n = 5) or a sham procedure (n = 5). Phase II included nine pigs, which were randomized to undergo embolization with smaller microspheres (100–300 μm) (n = 5) or a sham procedure (n = 4). All swine were administered 40 mg of oral omeprazole daily from 3 days before to 21 days after BAE or the sham procedure. Swine that had been fasted were sedated with injectable tiletamine-zolazepam (100 mg/mL) reconstituted with 2.5 mL of ketamine (100 mg/mL) and 2.5 mL of xylazine (100 mg/mL) at 1 mL per 25 kg intramuscularly, and anesthesia was induced with intravenous propofol (approximately 4 mg/kg). General anesthesia was maintained with isoflurane (Baxter Healthcare, Deerfield, Ill). Swine were intubated and mechanically ventilated.

BAE and sham procedures were performed with a sterile technique by an interventional radiologist (C.R.W., with 12 years of experience) and a veterinarian (D.L.K., with more than 20 years of experience). Femoral arterial access was obtained percutaneously with US guidance (Zonare Medical Systems, Mountain View, Calif), followed by placement of an introducer sheath (5 F). With x-ray fluoroscopic guidance (Axiom Artis Zee, Forchheim, Germany), a 5-F angiographic guide catheter (Flexion Axis, Surefire Medical, Westminster, Colo) was advanced over a 0.035-inch Bentson guidewire (Cook Medical, Bloomington, Ind) into the abdominal aorta to select the celiac axis. A pre-embolization celiac digital subtraction angiogram with iohexol injection (Omnipaque; GE Healthcare, Princeton, NJ) at 4 mL/sec for 5 seconds was obtained to map the vessels feeding the gastric fundus (Fig 1). A dual-phase cone-beam CT study with a 30% vol/vol iohexol injection at 4 mL/sec for 10 seconds was also acquired. An antireflux microcatheter (Infusion System mT, Surefire Medical) was then advanced over a 0.016-inch Fathom guidewire (Boston Scientific, Marlborough, Mass) into the fundal branches of the main gastric artery. One hundred micrograms of nitroprusside was delivered into that vessel, and the microcatheter was deployed. A cone-beam CT study with a 30% vol/vol iohexol injection at 2 mL/sec for 10 seconds was acquired in the fundal artery selected for embolization. The artery was then embolized with the microspheres diluted by 50% with iohexol until five beats of stasis in the target artery was achieved. Postembolization digital subtraction angiography and cone-beam CT were performed to confirm the success of embolization. The microcatheter was removed, flushed with saline, and repositioned before embolization of the next arterial branch. We embolized the right gastric artery and the left gastroepiploic artery in each animal in the BAE group (Fig 1). Control swine received saline in the corresponding gastric arteries.

Follow-up Examination

The pigs were weighed before BAE and every week thereafter, and fasting blood draws from the jugular vein were performed for plasma ghrelin measurement. Total plasma ghrelin concentration was assayed by using iodine 125–labeled bioactive ghrelin as the tracer and a rabbit polyclonal antibody (Phoenix Pharmaceuticals, Burlingame, Calif), as described previously (17,18). Endoscopy of the stomach was performed by an experienced human gastroenterologist (E.J.S., with more than 6 years of experience) 1 week after embolization and by using general anesthesia to assess the effect of the microspheres on the stomach mucosa with a standard adult gastroscope (Pentax, Denver, Colo). On the day before euthanasia, femoral arterial access was obtained as described above, and digital subtraction angiograms of the gastric arteries were acquired. All pigs were euthanized 16 weeks after BAE or sham procedures.

Gross Pathology

The stomach was removed from the abdominal cavity, retaining the distal esophagus and proximal duodenum. The excised stomach was opened along the greater curvature, washed, pinned flat, photographed, and fixed with 10% neutral buffered formalin. After fixation, the gastric mucosa was examined by a human pathologist (R.A.A., with more than 10 years of experience) for evidence of mucosal ulceration or injury. The pathologist was blinded to information regarding the study arms. Tissue blocks from representative parts of the stomach (gastric fundus, gastric body, antrum, and duodenum) were

taken from all pigs in approximately the same locations and were paraffin embedded for histologic analysis and toxicity assessment. Tissue blocks were cut from areas of mucosal ulceration if an ulcer was present.

Histopathologic Analysis

Hematoxylin-eosin staining was performed on 6-μm-thick slices from each representative part of the stomach; specimens were examined microscopically for mucosal integrity and the presence of microspheres. Adjacent slices were used for immunohistochemical detection of ghrelin-expressing cells (GECs) by using the primary mouse antighrelin antibody (1:5000, Millipore, Billerica, Mass). The bound ghrelin antibody was detected with streptavidin-labeled horseradish peroxidase and was visualized with diaminobenzidine chromogenic staining (Vector Laboratories, Burlingame, Calif). Images were captured at ×200 magnification by using an upright microscope (Eclipse Ti; Nikon Instruments, Melville, NY) and were analyzed by using NIS-Elements Basic Research, version 4.12 imaging software (Nikon Instruments). Ghrelin immunoreactive cell density was expressed as the mean number of positive cells per ×200 high-power field.

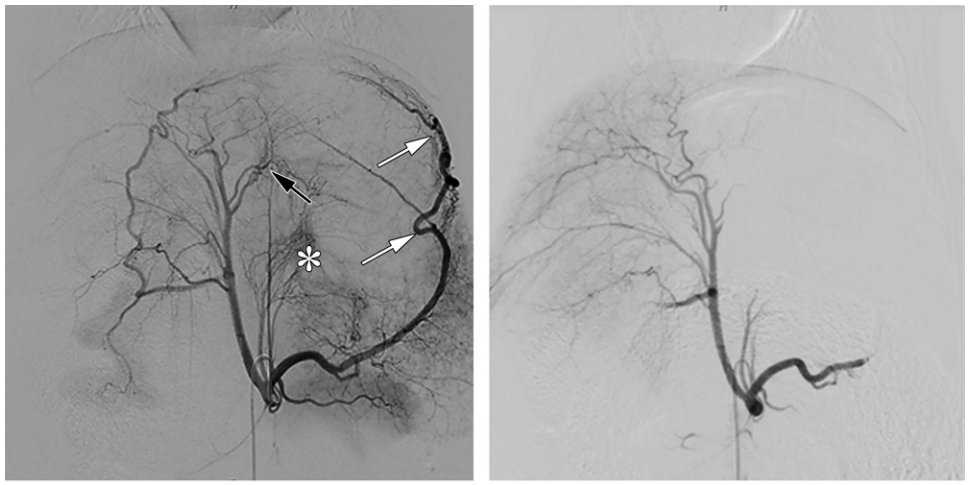


Figure 1: Representative celiac digital subtraction angiograms show procedures for bariatric swine arterial embolization. **(a)** Pre-embolization angiogram of the stomach shows the right gastric artery (black arrow), left gastric artery (*), and left gastroepiploic artery (white arrows) that supply the gastric fundus for embolization. **(b)** Postembolization angiogram after superselective embolization of the right gastric artery and the left gastroepiploic artery shows the stasis of blood flow.

Statistical Analysis

Data are presented as means ± standard deviations. Ghrelin-immunoreactive cell densities were compared by using the Wilcoxon rank-sum test. Weights were measured weekly for the first 2 months after BAE and then every other week until euthanasia at 16 weeks after BAE. For graphical representation, the mean percentage changes in weight, rather than absolute values, from baseline to weeks 1–16 were determined to better illustrate weight gain in growing pigs. Statistical testing for significant changes in weight gain and ghrelin plasma levels over time between BAE and sham pigs was performed by using a mixed-effects model and by including a fixed intercept and a random slope for each animal with time and treatment group as fixed effects. Differences at each time point were assessed by using this model, accounting for repeated measurements within each animal but assuming independence between treatment groups. $P < .05$ was considered to indicate a statistically significant difference. Statistical analysis was performed by using Stata, version 11 software (Stata, College Station, Tex).

Results

Selective bariatric embolization in the right gastric artery and left gastroepiploic artery was performed successfully in all animals that underwent BAE, regardless of the size of microspheres used. All pigs survived the 16-week study period with no clinically significant postprocedural adverse events.

Postembolization Weight Change

BAE-treated and control pigs showed a steady increase in weight gain during the 16-week study period (Figs 2, 3). However, pigs treated with smaller microspheres had significantly less weight gain relative to control animals ($P < .001$) (Fig 2). Mean percentage of weight gain from baseline to 12 and 16 weeks was 78.2% ± 20.9 and 107% ± 15, respectively, for BAE-treated pigs and 86.9% ± 9.5 and 131.9% ± 11.6, respectively, for control pigs. In contrast, mean weight gain at 16 weeks was not significantly different between pigs treated with larger microspheres (82.7% ± 14.8) and control animals (93.4% ± 7.5, $P = .85$) (Fig 3). BAE-treated pigs experienced less weight gain for the first 3 weeks relative to control pigs, but their weight gain gradually increased between weeks 4 and 8 after embolization.

Postembolization Plasma Ghrelin Values

Changes in total plasma ghrelin levels over time were not significantly different between control and BAE-treated pigs, irrespective of the size of the microspheres used (Fig 4). However, weekly mean plasma ghrelin levels were moderately lower in pigs treated with smaller microspheres than in control animals, except at week 5 (Fig 4a). For pigs treated with larger microspheres, there was no statistically significant difference in plasma ghrelin level changes compared with control pigs (Fig 4b).

Endoscopy

No control pigs had evidence of gastric mucosal injury. In contrast, all five pigs treated with smaller microspheres and three of five pigs treated with larger microspheres developed superficial mucosal ulceration in the targeted fundus or nontargeted

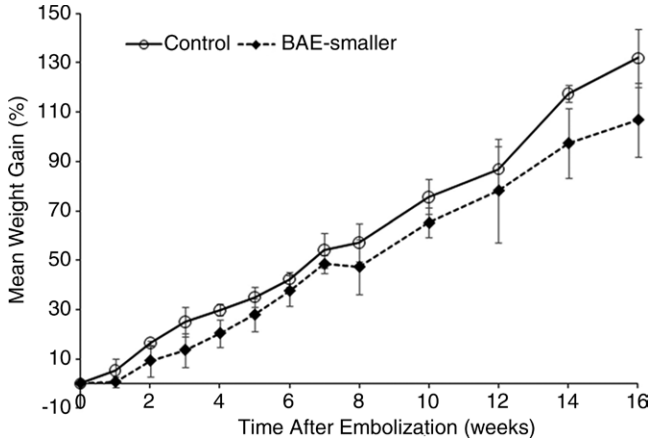


Figure 2: Graph shows mean percentage weight gains ± standard deviations after bariatric arterial embolization *(BAE)* performed by using 100- to 300-μm microspheres in five swine or after a sham procedure in four swine (control). Mean weight gain was statistically significantly lower in BAE-treated pigs than in control pigs. Weight gain of 100% indicates that weight doubled.

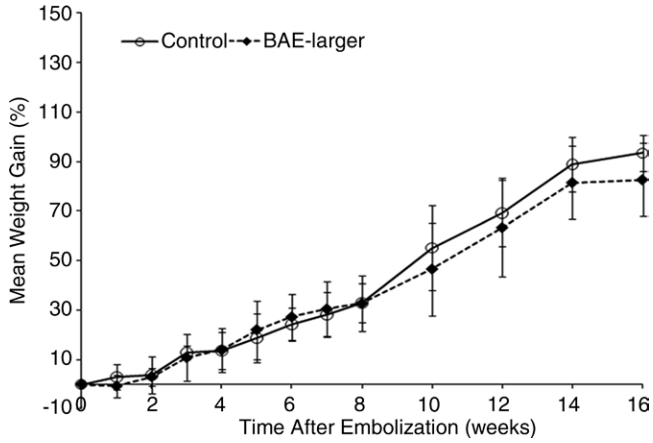


Figure 3: Graph shows mean percentage weight gains ± standard deviations after bariatric arterial embolization *(BAE)* performed by using 300- to 500-μm microspheres in five swine or after a sham procedure in five swine (control). There was no statistically significant difference in weight gain between BAE-treated and control groups at any time point.

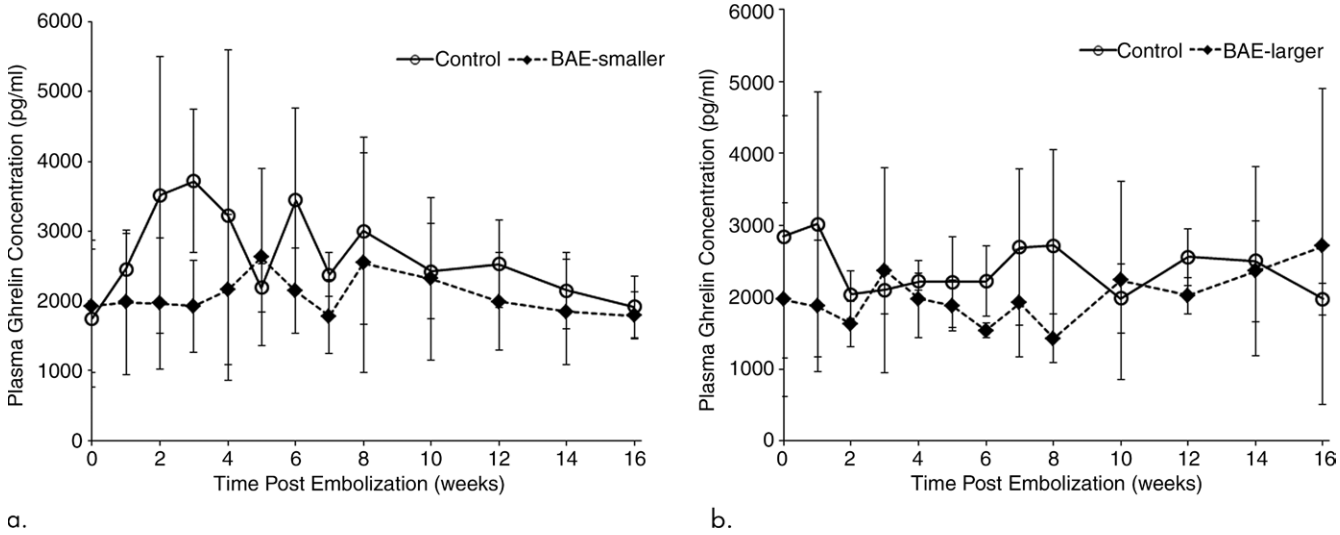


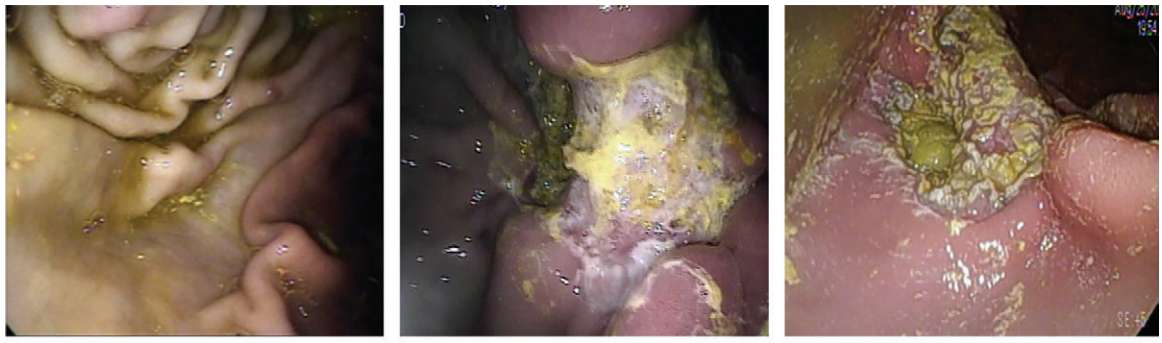
Figure 4: Graphs show weekly plasma ghrelin concentrations in swine that underwent bariatric arterial embolization *(BAE)* or a sham procedure. **(a)** Mean plasma ghrelin levels were lower in pigs treated with smaller (100–300-μm) microspheres than in control pigs; however, the differences were not statistically significant. **(b)** There was no statistically significant difference in mean plasma ghrelin levels between pigs treated with larger (300–500-μm) microspheres and control pigs.

gastric body along the lesser or greater curvature proximate to the fundus (Fig 5). These ulcers were mild and healing at 1 week after embolization. No ulceration was observed in the other parts of the stomach.

Histopathologic Analysis

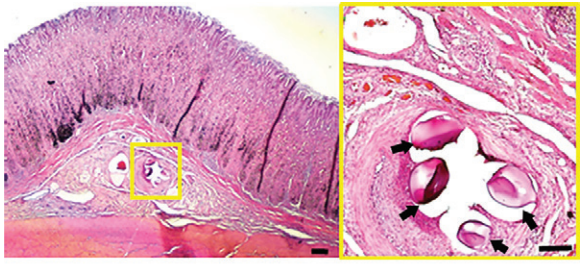
Histopathologic evaluation of the stomach showed the presence of smaller microspheres, restricted mainly within the submucosa and muscularis propria of the gastric body (Fig 6a), with lower concentrations in the fundus and antrum. In one animal, microspheres were also found in the duodenum (Fig 6b). In pigs treated with larger microspheres, no microspheres were identified in the analyzed tissues. No full-thickness ulcerations or perforations were noted in any BAE-treated animals that had mucosal ulceration at the 1-week endoscopic assessment.

There was no statistically significant difference in plasma ghrelin levels between BAE-treated and control pigs. However, there were significantly lower mean densities of ghrelin immunoreactive cells (number of positive cells per ×200 high-power field) within the gastric fundus (14.8 ± 6.3 vs 25.0 ± 6.9, $P < .001$) and body (27.5 ± 12.3 vs 37.9 ± 11.8, $P = .004$) in pigs treated with smaller microspheres than in control pigs. The ghrelin immunoreactive mean cell densities in the gastric antrum (28.2 ± 16.3 vs 24.3 ± 11.6, $P = .84$) and duodenum (9.2 ± 3.8 vs 8.7 ± 2.9, $P = .66$) were not significantly different between pigs embolized with small microspheres and control pigs (Fig 7). In contrast, there was no statistically significant histologic difference in ghrelin immunoreactive cell density in any part of the stomach for pigs treated with larger microspheres compared with control pigs (fundus: 9.1 ± 5.8 vs 11.7 ± 6.8,

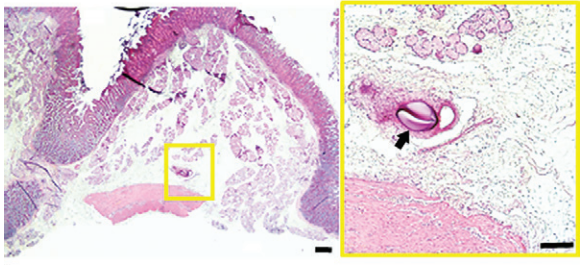


a. b. c.

Figure 5: Endoscopic images of swine stomachs 1 week after embolization. **(a)** Representative image of the stomach of a control pig. **(b)** Image of a stomach embolized with smaller (100–300-μm) microspheres shows ulceration in the gastric body proximal to the fundus. **(c)** Image of a stomach embolized with larger (300–500-μm) microspheres shows superficial ulceration in the gastric body. All ulcers were mild and had healed by week 16.



a.



b.

Figure 6: Histopathologic evaluation of the distribution of 100- to 300-μm microspheres in hematoxylin-eosin–stained stomach sections of one pig that underwent bariatric arterial embolization shows **(a)** microspheres in the submucosa of the gastric body (arrows) and **(b)** microspheres in duodenum (arrows). Insets = ×5 magnified views of the microspheres. Bars = 200 μm.

P = .96; body: 29.0 ± 13.0 vs 25.8 ± 6.6, P = .44; antrum: 10.4 ± 7.0 vs 15.3 ± 12.0, P = .92; and duodenum: 8.2 ± 5.0 vs 8.0 ± 4.0, P = .76) (Fig 8).

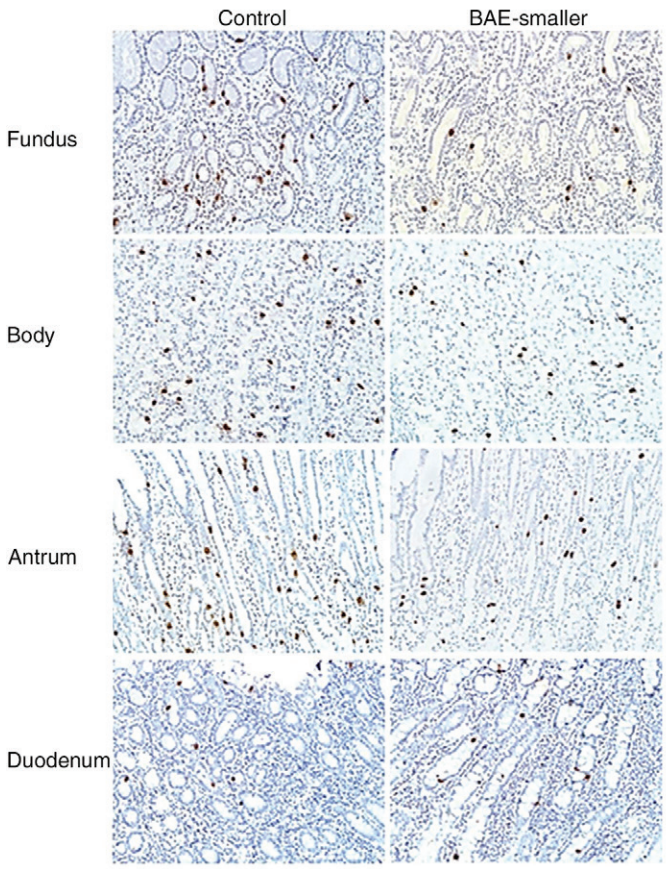
Discussion

Our findings suggest that BAE with smaller embolic microspheres may be more effective at reducing long-term weight gain and suppressing fundal ghrelin expression than sham treatment but may cause more gastric ulceration. Larger embolic microspheres were not effective compared with sham treatment for the measured variables.

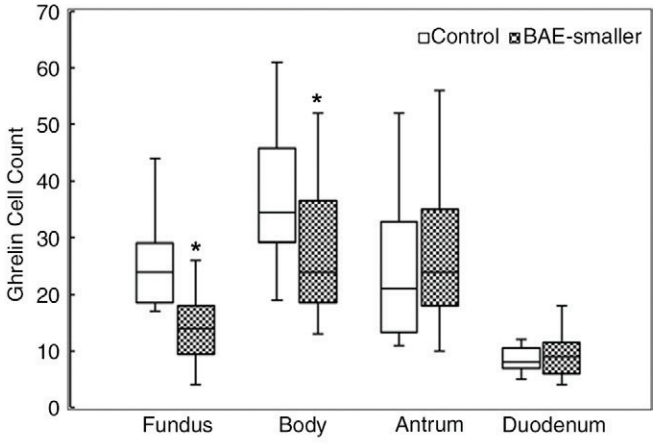
Since its discovery in the rat stomach, ghrelin has been recognized as the only hormone that potently stimulates hunger (25–27). Strategies have been designed to suppress the effect of ghrelin on the central nervous system, resulting in weight loss and reduced food intake in animals (28,29). In patients with obesity, GECs have much higher density and expression levels in the gastric mucosa than in normal-weight individuals (30). Such high concentration of GECs in the stomach makes ghrelin-targeting interventions conceivable by gastric artery embolization.

Arepally et al (17) reported a proof-of-concept study in swine using liquid sclerosant (morrhuate sodium) to modulate ghrelin production. The suppression of systemic ghrelin levels from high doses of sclerosant was thought to be attributed to maximum ischemic stunning by the distal penetration of liquid embolic agent. However, liquid sclerosing agents are toxic and difficult to deliver accurately (17,19). Insoluble biocompatible embolic particles are currently used for both oncologic and nononcologic applications (19,20,24,31–33). In animal studies, bariatric embolization with embolic particles has resulted in decreased serum ghrelin levels, statistically significant weight loss (19), or reduced weight gain (20,32) at up to 8 weeks. Gastric ulceration was noted in nearly half of a very small number of pigs (n = 5 or 6) embolized with small (40-μm) or intermediate-sized (50- to 250-μm) particles, regardless of the number of vessels embolized (20,32,34). No adverse events or gastric ulceration was observed in animals embolized with larger (500- to 700-μm) particles (19,21).

The significantly lower mean weight gain we observed in animals embolized with smaller microspheres was correlated with marked suppression of GECs in the gastric fundus and body. In contrast, larger microspheres failed to suppress weight gain or ghrelin expression in any part of the stomach. No embolic particles were detected in swine that received larger microspheres, suggesting that the larger particles did not penetrate deeply into the gastric mucosa, where ghrelin cells are abundant. Similar serum ghrelin levels were noted between animals treated with small or large microspheres and control animals. This is in contrast to the findings of early studies that used liquid sclerosant or 40-μm particles (17,18,34) but is consistent with the findings of a recent study (32) that used nonspherical intermediate-sized polyvinyl alcohol particles. In theory, liquid sclerosant or smaller microspheres provide a more distal embolization and reduce the chance of collateral perfusion compared with larger microspheres; this suggests that smaller microspheres may cause



a.



b.

Figure 7: **(a)** Immunohistochemical stains of ghrelin-immunoreactive cells in the stomachs of swine that underwent bariatric arterial embolization *(BAE)* with 100- to 300-μm microspheres or a sham procedure. **(b)** Boxplot of ghrelin cell counts shows statistically significant reduction of ghrelin-expressing cells in the gastric fundus ($P < .001$) and body ($P = .004$) without compensatory upregulation in the duodenum ($P = .66$) and antrum ($P = .84$) after BAE with 100- to 300-μm microspheres or a sham procedure.

more ischemia to the stomach, leading to greater suppression of ghrelin production.

The BEAT Obesity trial, using 300- to 500-μm microspheres, reported 9.0% mean excess weight loss at 3 months (24), which is similar to our observed difference of reduced weight gain (8.7%) between pigs treated with smaller microspheres (78.2%) and control pigs (86.9%) at 12 weeks. One can infer that the embolization achieved with smaller microspheres in swine may correspond to that of larger microspheres in humans with parallel differences in vessel size between adult humans and juvenile swine.

Percutaneous transarterial embolization is a minimally invasive procedure performed routinely by interventional radiologists for treating upper gastrointestinal artery bleeding (35,36) and is typically well tolerated. We observed superficial gastric ulceration in all animals embolized with smaller microspheres and in three of five animals embolized with larger microspheres, suggesting that more-distal bariatric embolization with smaller microspheres may increase the risk of gastric ulceration. Most ulcers were in the gastric body, which was confirmed at pathologic examination, suggesting that non-target embolization occurs. The use of a Surefire antireflux catheter instead of a standard end-hole catheter, although it prevents reflux, may pressurize the system such that communicating vessels in the swine stomach may be embolized, leading to non-target bead deposition. Additionally, the ulceration rate we observed might be explained by the timing of endoscopy at 1 week after embolization instead of at 3 weeks, as reported in other preclinical studies (21,32). Taken together, appropriate embolic particle size should be considered to balance embolization efficacy and safety before clinical translation.

There were several limitations to our study. Our study used young, healthy, growing swine and not obese, adult swine to minimize confounding variables and provide comparable metrics to earlier studies (18,20). Because of the physiologic differences between growing swine and obese adults, future research should test the effect of embolic size on hormone and weight change in obese subjects. Ghrelin regulation is a dynamic process. Circulating ghrelin exists in two forms: acyl ghrelin and des-acyl ghrelin, and only acyl ghrelin can bind and activate the growth hormone secretagogue receptor type 1a (26). However, the serum ghrelin assay we used cannot differentiate active acyl ghrelin from inactive des-acyl ghrelin. Future studies of the effect of BAE on acyl or des-acyl ghrelin production may be warranted. The lack of a statistically significant difference in total serum ghrelin levels between embolized and control pigs may be explained by the natural variation of ghrelin levels throughout the day, given that the blood draws could not be performed in all animals at the exact same time of day. Additionally, the fasting serum ghrelin levels that we assessed might also have been affected by the fact that our animals were socially housed with exposure to feedings of other, non-fasting animals (37). The lack of correlation between fundal ghrelin cell expression and plasma ghrelin levels suggests that strict control of blood draws and animal housing, as well as assays to assess inactive versus active forms of ghrelin, may be needed for plasma ghrelin level assessment.

In conclusion, smaller embolic microspheres appear to be more effective than larger microspheres in reducing weight gain and suppressing fundal and gastric body ghrelin expression without compensatory upregulation of GECs in other parts of the stomach for up to 16 weeks. However, the high ulceration rate in

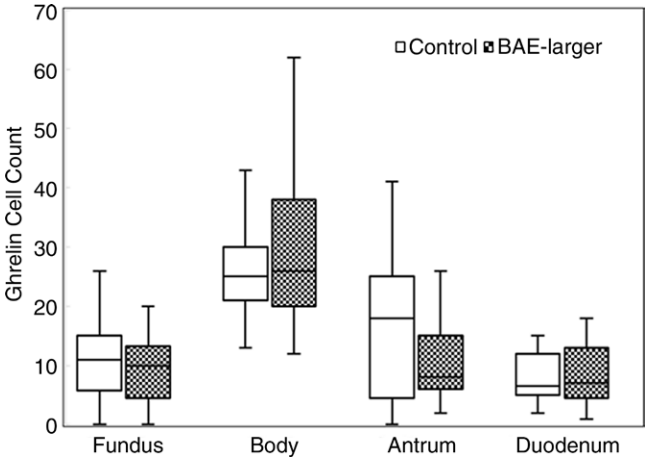


Figure 8: Boxplot of ghrelin cell counts shows similar ghrelin-expressing cell densities in all parts of the stomach between pigs that underwent bariatric arterial embolization *(BAE)* with 300- to 500-μm microspheres and those that underwent a sham procedure.

pigs embolized with smaller microspheres highlights the need to balance safety and efficacy when choosing embolic particle size before clinical translation.

Practical applications: BAE with smaller microspheres may be an effective, minimally invasive approach for the treatment of obesity.

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